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Toward Targeted Hypertension Screening Guidelines

Stef van Buuren, PhD, Hendriek C. Boshuizen, PhD, Sijmen A. Reijneveld, MD

Background. Guidelines for screening and subsequent treatment of hypertension vary widely between countries. Part of this variation can be attributed to systematic differences between populations, but little is known about the way in which guidelines should be targeted to the population of interest. Optimal guidelines should have high yield and low complexity. The goal is to fit procedures for screening and subsequent treatment of hypertension optimally to a specific population. **Methods.** Simulation study on individual cardiovascular risk profiles, with drug treatment altering the 10-year cardiovascular risk. The analysis compares the consequences of various screening and treatment alternatives. The reference scenario consists of the Dutch hypertension guidelines for primary care. A representative sample of the Dutch population aged 20 years and older is taken as the target. Main outcome measures include incidence, quality-adjusted life years

won, number needed to screen, and costs (prevention, morbidity, and mortality). The discount rate is 4%. **Results.** Strict adherence to the current hypertension guidelines saves costs (i.e., the total prevention costs are less than the costs of prevented morbidity and mortality). The following changes increase its cost-effectiveness: use of lower blood pressure levels for screening and treatment, reduction of the number of screens from 5 to 3, and active call-up of high-risk patients. The adherence to guidelines has a large influence on actual cost-effectiveness achieved in practice. **Conclusions.** Appropriate targeting of hypertension guidelines to a population and critical appraisal of the entire screening procedure can enhance cost-effectiveness. **Key words:** hypertension; risk factors; mass screening; practice guideline; guideline adherence; health care costs. (*Med Decis Making* 2006;26:145-153)

Treatment of hypertension reduces risks of cardiovascular disease and thus yields future health gains. Over the past decade, expert committees in many countries developed guidelines for screening and treatment of those at high risk. Important discrepancies between these recommendations have, however, been signaled.¹⁻⁴ Recommendations seriously diverge on the levels of blood pressure (BP) that define hypertension. Also, they vary in the set of risk factors that must be taken into account, the number of visits needed for diagnosis, the age at which to start screening, the minimum BP level that justifies drug treatment, the therapeutic objectives, and so on.

Following the classic work of Stason and Weinstein,⁵ cost-effectiveness of hypertension treatment has been studied quite extensively.⁶⁻¹⁰ The results from these studies are extremely helpful in making clinical guidelines more evidence based. Screening has attracted less attention, however. Published guidelines are usually very brief on screening, and little systematic research on appropriate screening strategies is available. Ramsey and others² highlighted the role of the absolute cardiovascular risk of the population in the context, but most cost-effectiveness studies do not account for the population risk. The implication is that

cost-effectiveness of the same screening strategy may vary dramatically with the risk of the population. Furthermore, it is common practice to screen patients for

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having cardiovascular risk factors, which widely vary in both prevalence and associated risks. Thus, selection and exclusion may highly affect cost-effectiveness. Finally, little is known about the impact of choices made in the screening procedure on cost-effectiveness, such as the number of screens needed for diagnosis, the age at which screening should start, and appropriate BP cutoff levels for best cost-effectiveness.

This study presents the results of an approach to fill these gaps. Our approach accounts for the risk factor distribution in the population of interest and enables us to study the influence of different screening alternatives on cost-effectiveness. We applied our method to the Dutch population, aged 20 years and older, departing from Dutch hypertension guidelines.¹¹ This is one of the few guidelines that contains a relatively detailed screening protocol. More specifically, we concentrated on 2 questions: Are the current hypertension guidelines cost-effective for the population of interest? Is it possible to improve cost-effectiveness by altering the screening procedure?

METHOD

Model

We developed a simulation model that enabled us to define variations on the published guidelines, called scenarios. Each scenario was applied to a representative sample of persons from the population of interest. The cardiovascular risk profile of each person was known.

Cardiovascular risk factor data on the Dutch population were available from the MORGEN study¹² (ages 20–59, $n = 13,742$, collected in 1995–1997) and the Rotterdam study¹³ (ages 55+, $n = 7983$, collected in 1990–1993). Measurements include systolic (SBP) and diastolic (DBP) blood pressure, low-density lipoprotein (LDL)/high-density lipoprotein (HDL) ratio, diabetes, cardiovascular history, familial cardiovascular disease, left-ventricular hypertrophy, smoking, body mass index (BMI), and use of alcohol. We drew a resample of 11,983 people from the combined data such that age and sex distributions corresponded to the Dutch population of 20 years or older per 1 January 2000. Each person in the simulation sample thus corresponded to 1000 real people in the population. The appendix describes some practical data problems that had to be dealt with.

The model computes the 10-year absolute coronary risks for 7 events: death by coronary heart disease (CHD), death by other cardiovascular disease (CVD), death by non-CVD, myocardial infarct (MI), other CHD,

stroke, and other CVD. In line with other work,¹⁴ the incidence rates predicted by the equations from the Framingham Heart Study¹⁵ were generally very close to Dutch incidence data. Some minor adjustments were needed for the older age groups, in which the Framingham predictions were often too low (see the appendix for more details). We assumed that antihypertensive drug treatment induces proportional reductions in the absolute risk that varies between 13.7% (for CHD mortality) and 34.3% (for stroke)¹⁶ (see the appendix for more details).

BP measurements were randomly simulated under a statistical model for blood pressure variation, similar to the model used by Rosner and Polk.¹⁷ The mean of the distribution from which measurements were drawn depended on the set of risk factors particular to the person. The variance of the distribution consisted of 4 components: between persons (variances SBP: 400.5, DBP: 94.1), between visits (variances SBP: 105.6, DBP: 23.7), between doctors (variances SBP: 6.1, DBP: 5.1), and within visits (variances SBP: 26.0, DBP: 16.3). More details about the BP model and the estimates can be found elsewhere.¹⁸

Costs and Health Effects

Costs were estimated for screening, preventive treatment, mortality, and morbidity. Screening and preventive treatment occur in a primary care setting. Screening costs depend on the number of patient visits, the fee per visit (€18.15), and laboratory costs (€11.34 per case). The fee per visit and the laboratory costs were based on the actual reimbursement scheme of the Dutch health system. Costs of antihypertensive treatment were equal to €190.59 per year per treated patient.¹⁹ Estimates of morbidity and mortality costs were taken from Van Hout and others¹⁰ and are given in the appendix. The same estimates have been used to assess cost-effectiveness of the Dutch cholesterol guidelines.¹⁰ Costs are reported in euros (€) per person (in the population) per year (pppy) in prices of the year 2000. Prices of previous years were corrected for inflation to 1 January 2000 using the official inflation rates as published by the Netherlands Bureau of Statistics. Total yearly costs on the population level were found by multiplying estimates made in terms of “€ pppy” by a constant 11,983,000, the size of the population aged 20 years and older. An expert committee reviewed all cost estimates used within the project.

The following health outcomes were estimated under each scenario: incidences (for all 7 risk events), number needed to screen (NNS) and number needed to treat (NNT) to prevent 1 cardiovascular event,²⁰ life

Table 1 Overview of Variations (Scenarios) on the Dutch Guidelines

Scenario	Description
basic	Basic scenario: screening and treatment according to the Dutch guidelines
freeze	No further screening and case finding (null model)
50+	Lowers the minimal screening age to 50
55+	Lowers the minimal screening age to 55
65+	Increases the minimal screening age to 65
-dia	Eliminates diabetes as an entrance criterion
-fam	Eliminates familial cardiovascular disease as an entrance criterion
-his	Eliminates earlier cardiovascular history as an entrance criterion
+bmi	Adds body mass index ≥ 30 as an entrance criterion
+smo	Adds smoking as an entrance criterion
+alc	Adds daily use of alcohol as an entrance criterion
active	Actively calls up patients satisfying entrance criteria to entrance consult
any	Ignores any entrance criteria, measures blood pressure (BP) of all patients attending the consult
3visits	Lowers the maximum number of follow-up consults from 5 to 3
E150/90	Lowers the BP criterion for follow-up measurements 1 to 3 from 160/95 to 150/90
E140/85	Lowers the BP criterion for follow-up measurements 1 to 3 from 160/95 to 140/85
V150/90	Lowers the BP criterion for follow-up measurements 4 and 5 from 160/95 to 150/90
I160/95	Lowers the BP criterion for drug treatment without risk factors from 180/105 to 160/95

years gained, quality-adjusted life years (QALY) gained, and healthy life years gained. Utility values for the QALY calculations were taken from the literature.²¹ The appendix details how these are calculated.

Screening took place during the 1st year. We assumed that drug treatment, if indicated, lasted for the full 10 years and only stopped if the patient died. The official Dutch discount rate of 4% was used to adjust for time preference in both costs and health.²² To eliminate the influence of tiny improvements among many people with normal blood pressure, life year measures were calculated under the assumption that drug treatment has no effect below a sustained blood pressure level of SBP <160 mm Hg and DBP <90 mm Hg.

Analysis

The starting model was based on the Dutch hypertension guidelines. The guidelines define hypertension as sustained SBP >160 mm Hg or DBP >95 mm Hg. The screening protocol is as follows. The general practitioner should measure the BP of all visiting patients with an increased cardiovascular risk. This concerns patients with 1 of the following screening factors: diabetes mellitus, previous CHD, older than 60 years, familial CVD, indication for cholesterol treatment, or earlier hypertension. If the initial BP is above 160/95 mm Hg, then BP should be measured during 3 additional visits. If either the average SBP is <160 and DBP is <95, or if

DBP is >105, no further measurements are taken. Two additional visits are scheduled for the remaining group. Drug treatment is indicated if mean DBP >105 or mean SBP >180 mm Hg. If 1 or more additional risk factors (high cholesterol, diabetes mellitus, smoking, organ damage, familial CVD, age >60, male) are present, drug treatment is indicated if DBP >100 or SBP >160. After appropriate titration of dosage, control visits have to occur once every 3 months. Patients with known and treated hypertension do not enter the screening. Only patients who visit the general practitioner are measured; there is no active call-up.

We first assessed the effect of the Dutch guidelines (scenario “basic”) compared to the situation in which the entrance of all new cases stopped but known cases continued treatment (scenario “freeze”). Comparing scenarios “basic” and “freeze” provides evidence about the cost-effectiveness of the Dutch guidelines compared to doing nothing. Although the “freeze” scenario is unlikely to occur in practice, it provides a natural null for the health effect measures and screening costs. The comparisons of real interest are between the “basic” scenario and simple variations in the guidelines, as defined in Table 1. This comparison yields insight into the performance of separate components of the current guidelines. Many aspects of the results can be inspected. To be concise, the Results section focuses on the QALYs gained under each scenario. The QALY summarizes effects on both mortality and morbidity by

combining the length of life and utility (i.e., quality) of the life years concerned.

In practice, adherence to the guidelines is imperfect, which could influence the actual cost-effectiveness seen in practice. To study the impact of imperfect adherence, we conducted additional analyses in which persons indicated for treatment were randomly assigned to the nontreatment group (under-treatment), and persons not indicated for treatment were randomly assigned to the treatment group (over-treatment).

RESULTS

Figure 1 is a graphic representation of the screening procedure according to the Dutch guidelines. The figure portrays the flow of the Dutch population age 20 years and older on 1 January 2000 through this procedure. Screening and detection of hypertension consist of 6 steps, represented in the central column of Figure 1. At the end of the screening year, the outcome (indicated for treatment, yes/no) is known for every population member. The total number of new cases indicated for drug treatment is equal to $34,000 + 249,000 = 283,000$, or about 2.4% of the population.

Table 2 presents incidence rates, costs, and health effects of the Dutch guidelines ("basic") compared with doing nothing ("freeze"). According to the table, prevention decreased the total yearly cardiovascular morbidity by about 2314 new cases (1.8% of the total morbidity), particularly through a reduced incidence of stroke. The number of deaths decreased by 1052 per year, or about 0.7% of the all-cause mortality. For comparison, this is similar to the yearly number of traffic deaths in the Netherlands. The total number of life years gained for treating the 283,000 patients de novo is equal to 63,968 years (undiscounted 95,216 years), which corresponds to 3 months of additional life expectancy per treated patient. Gains in QALYs (110,964) are larger because the effect of drug treatment on morbidity is larger than on mortality.²³ The total costs under the basic scenario were estimated as €264.26 pppy, or about €3.17 billion per year for the population age 20 and older. Stopping all screening activities lowered prevention costs by €6.40 pppy ($= 0.81 + 5.59$). However, as more disease occurred, morbidity costs without prevention were €7.10 pppy ($= 6.92 + 0.18$). Thus, prevention through strict adherence to the guidelines pays for itself and comes with a positive balance of €0.70 pppy. The increased (healthy) life expectancy is a bonus.

The 2nd question is how the current guidelines can be improved. Figure 2 plots the QALYs gained against the costs. Observe that the variations in costs are very

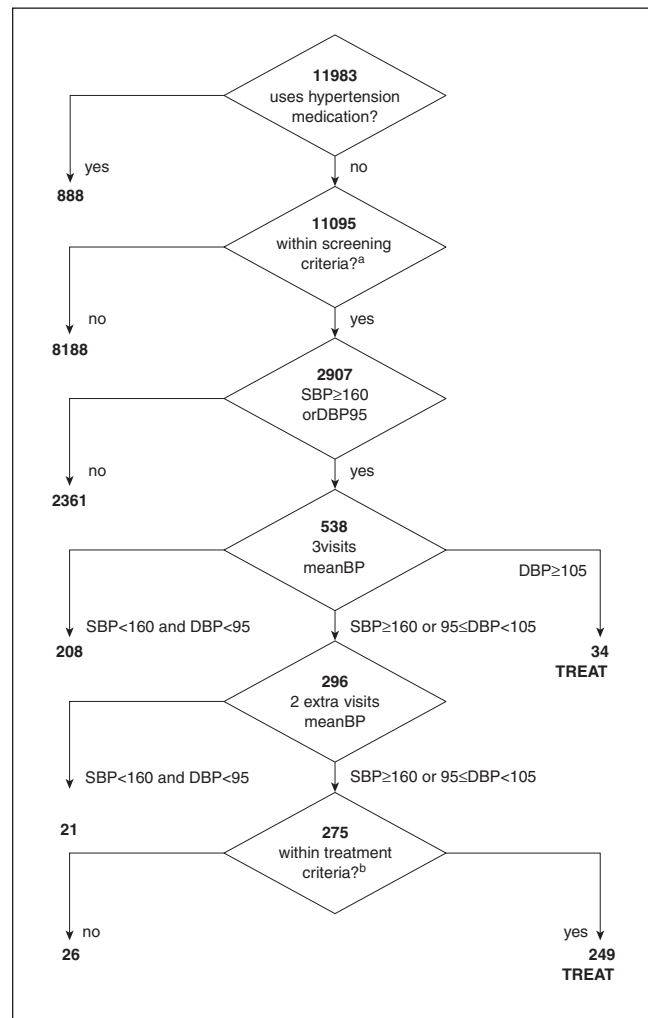


Figure 1 Flow diagram for hypertension screening according to the current Dutch hypertension guidelines (numbers are in thousands).

a. Screening criteria: diabetes, previous CHD, age > 60, familial CVD, high cholesterol, history of hypertension.

b. Treatment criteria: DBP ≥ 105, SBP ≥ 180, 160 ≤ SBP < 180 with risk factor, 100 ≤ SBP < 105 with risk factor. Risk factors are: high cholesterol, diabetes, smoking, organ damage, familial CVD, age > 60, male.

small (within 1%), whereas differences in health outcomes vary by more than 40%. The most cost-effective scenarios are located in the upper-left corner. Scenario "active," which involves an active approach of potential high-risk patients, had the most favorable cost-effectiveness ratio and in fact dominates the basic scenario. Other scenarios that improved the cost-effectiveness (compared to the current guidelines) concern a lowering of the BP critical cutoff levels for follow-up or treatment (E140/85, E150/90, V150/90, I160/95). Thus, the level for the entrance visit in the current guidelines may be too high. Reducing the maximum number of follow-up visits from 5 to 3 could be done without adverse effects and even slightly improves

Table 2 Estimated Absolute Incidences, Health Effects, and Costs in the Dutch Population 20 Years and Older ($N = 11,983,000$) under Scenarios “Freeze” (Stop All Screening Activities) and “Basic” (Strict Adherence to the Current Guidelines)

Outcome	Scenario		
	Freeze	Basic	Difference
Incidence (events per year)			
Myocardial infarct	26,304	25,942	362
Other coronary heart disease (CHD)	15,752	15,624	128
Stroke	31,627	30,310	1317
Other cardiovascular disease (CVD)	54,402	53,895	507
Total morbidity	128,085	125,771	2314
Mortality by CHD	27,980	27,578	402
Mortality by other CVD	21,130	20,480	650
Non-CVD mortality	101,371	101,371	0 ^a
Total mortality	150,481	149,429	1052
Health effects			
Number needed to screen (NNS) morbidity	∞^a	503.0	
Number needed to treat (NNT) morbidity	∞^a	12.1	
Life years gained	0 ^a	63,968	
Quality-adjusted life years (QALYs) gained	0 ^a	110,964	
Healthy life years gained	0 ^a	174,684	
Costs (in euros per person age 20 and older per year)			
Screening	0	0.81	-0.81
Treatment and control	17.59	23.18	-5.59
Cardiovascular morbidity	233.21	226.29	6.92
Cardiovascular mortality	14.17	13.99	0.18
Total cost	264.96	264.26	0.70

a. By definition.

upon cost-effectiveness. A reduction in the number of visits would simplify the lower part of the flowchart in Figure 1. Using risk factors (obesity, smoking, or alcohol) as additional entrance criteria also improved effectiveness but at increasing costs. It is generally more efficient to lower the age at which screening should start. Compared to other scenarios, it was not cost-effective to measure the BP of all patients, regardless of age, who visit the general practitioner (scenario “any”). Using (healthy) life years instead of QALYs led to similar findings.

Combining the best scenarios from Figure 2 yielded additional benefits. Compared to the basic scenario, we found that 1) lowering the entrance criterion from 160/95

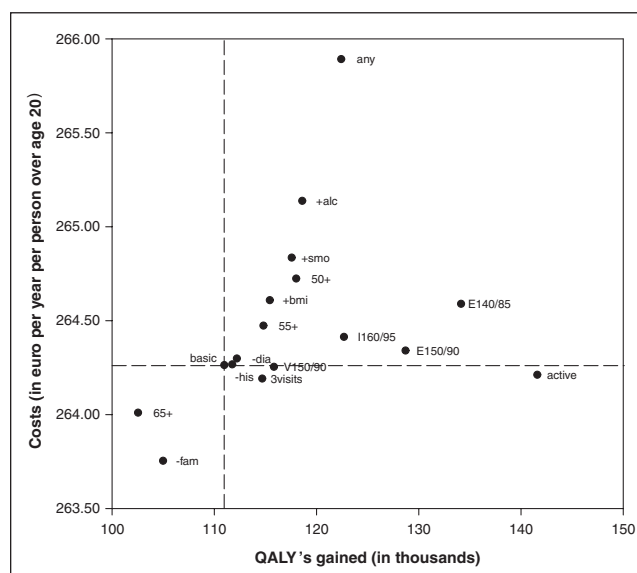


Figure 2 Total quality-adjusted life years (QALYs) gained in the Dutch population age 20 and older plotted against the total costs (in euros per person per year). See Table 1 for abbreviations of scenarios.

to 140/85 and 2) using only 3 follow-up visits slightly reduced costs (€264.21 pppy instead of €264.25 pppy) and substantially increased QALYs won (138,800 instead 110,964). Thus, the combination of 2 simple alterations led to a much better screening method. If, in addition, the criterion for drug treatment for patients with no extra risk factors was lowered from 180/105 mm Hg to 160/100 mm Hg, then the number of QALYs won increased to 167,000 at slightly higher costs (€264.85 pppy). Combining this with the scenario “active” boosted cost-effectiveness even further (197,400 QALYs, €265.48 pppy). These results demonstrate that (much) larger health benefits are possible than achieved with the current guidelines, at only small increases in costs.

We conducted an additional analysis in which we randomly assigned 50% of the group with high BP to the nontreatment group. The realized health gains were approximately only half of the potential gains at almost equal costs. Over-treatment led to the opposite effect. We took a random sample of 5% of the population that was not indicated for drug treatment and assumed that this group was treated with BP-lowering drugs. The health benefits of treating this group were relatively small, but the costs increased dramatically.

DISCUSSION

Are the Dutch hypertension guidelines cost-effective? Can we improve on the cost-effectiveness of the guide-

lines and, if so, at what points? We found that strict adherence to the guidelines is a cost-effective way of preventing cardiovascular disease. Substantial improvements can be achieved by altering specific screening and treatment criteria. In particular, the following changes increase the cost-effectiveness for the Dutch population age 20 years and older: use of lower blood pressure levels for screening and treatment, reduction of the number of consultations from 5 to 3, and active call-up of high-risk patients.

Although the analyses done with respect to adherence are somewhat crude, they clearly indicate that cost-effectiveness in real life can be quite different. We are therefore cautious to interpret our estimates only within the context of "strict adherence to the guidelines." On the other hand, we observed that the relative positions of the scenarios remained largely unchanged in these analyses.

During the course of this study, a revision of the hypertension guidelines appeared.²⁴ This update proposed a similar screening strategy as in Figure 1 but with using a lower minimal entry-level criterion, 140/90 mm Hg instead of 160/95 mm Hg. In addition, the minimum BP level for drug treatment was lowered to 140/90 mm Hg for patients with an absolute mortality risk over 10 years over 20%. As these changes implement some of our best scenarios, it is to be expected that the updated guidelines will have improved cost-effectiveness.

What can we say about other standards?²⁵⁻²⁷ Compared to others, the Dutch guidelines are quite conservative. Our results indicate that they might be in fact too conservative and miss important health gains by setting the levels for screening and treatment too high. The British guidelines recommend BP measurement of all adults at least every 5 years until the age of 80 years, as well as annual remeasurements of those with high-normal values (135–139/85–89 mm Hg) or with high readings at any previous measurement.²⁵ This selection of persons is akin to scenario "any," the scenario that

we found to be the most expensive and most liberal. Assuming the UK population is not too different from the Dutch population, this suggests that using a more selective set of screening criteria could improve the cost-effectiveness of the British guidelines. For some groups, the new US guidelines²⁶ prescribe drug treatment at BP levels as low as 130/80 mm Hg. It is possible to adapt our methodology to these guidelines, so that the model can be rerun on US or British data. The Dutch model defined a level of 160/90 mm Hg under which the effect of drug treatment on risk is considered to be zero. This parameter would obviously need to be adjusted to bring out the risk-reducing effects of drug therapy for people with lower risks.

There are many reasons why the optimal country-specific guidelines may differ from each other. Large international differences exist in cardiovascular risk profiles,^{28,29} demographic composition, pricing of medication, policies regarding drug treatment, organization of the health care system, disease incidences, disease costs, and so on. The existence of an optimal set of universally applicable guidelines is unlikely. Our method provides a way to account for the risk profile of a population, as well as for characteristics of the local health services. In general, both characteristics need to be taken into account in the development of guidelines.

CONCLUSION

Appropriate targeting of hypertension guidelines to a population and critical appraisal of the entire screening procedure can enhance cost-effectiveness of this screening. The method as described is flexible and enables appropriate targeting of hypertension guidelines to a population and critical appraisal of the entire screening procedure. Its added value in the improvement of screening procedures for other health problems deserves additional study.

APPENDIX

This appendix contains further details of the simulation model designed for this study. The general idea is as follows. The model describes the route taken by an individual patient under a given scenario for screening and subsequent treatment of hypertension. Individual outcomes vary as a result of differences in individual risk factors, differences between scenarios, differences that emanate from the random allocation to treatment and nontreatment groups (only for scenarios modeling under- and over-treatment), and differences that occur as random variation in the simulated BP measure-

ments. The model assumed that screening occurs in the year 2000. The model estimates mortality and morbidity risks and all costs for all individuals during the period 2000–2009. Aggregation over individuals and time allows for the estimation of costs and health effects in subgroups and in the population at large. Costs and health effects can also be compared across different scenarios for screening and subsequent intervention. Systematic comparison of different scenarios yields insight into the most optimal scenarios for the population at hand.

Table 3 Endpoints of the Framingham Equations, Correction Factors Used to Calibrate the Equations to the Dutch Incidence Data, and the Estimated Risk Reduction

Name	Endpoint Description	Calibration Factor	Calibration Group	Risk Reduction
CHDD	Coronary heart disease death	None		0.857
CVDD	Cardiovascular disease death	None		0.803
CHD	Coronary heart disease	1.02549 ^{^(age-60)}	60+ females	0.838
MI	Myocardial infarction	1.04091 ^{^(age-60)}	60+ females	0.838
STROKE	Stroke, including transient ischemic attack	1.03888 ^{^(age-50)}	50+ males	0.657
		1.03811 ^{^(age-50)}	50+ females	
CVD	Cardiovascular disease	None		0.775

Note: Symbol “^” stands for the power operator.

The model consists of 4 major components:

1. A data set of persons representative for the population
2. A set procedures for screening and subsequent treatment of hypertension (scenarios)
3. A risk model for future mortality and disease for every person
4. A set of rules for calculating costs and health outcomes

The text below provides additional details of each component.

Cardiovascular risk factor data from the MORGEN study¹² (ages 20–59, $n = 13,742$) and the Rotterdam study¹³ (ages 55+, $n = 7,983$) were used. A combined data set was constructed, but several practical problems had to be dealt with. First, we observed large differences (about 8 mm Hg) between the mean DBP levels of the MORGEN and Rotterdam data at the ages of overlap (55–59 years), whereas no such differences were present for SBP. Because it is desirable that the BP levels connect at the joint ages and because the DBP levels of the Rotterdam data were relatively low (about 73 mm Hg), we corrected for this difference by adding 8 mm Hg to all SBP measurements from the Rotterdam study. A 2nd problem was that dismissing incomplete records from the Rotterdam data would result in a severe reduction of the available information (from 7983 to 4360 individuals). We addressed this problem by multivariate imputation. Incomplete continuous factors (SBP, DBP, LDL/HDL ratio) were imputed by linear regression, incomplete binary factors (smoking, diabetes, cardiovascular history, familial cardiovascular disease, left-ventricular hypertrophy, already being treated for hypertension, use of alcohol) were imputed by logistic regression, and incomplete polytomous variables (BMI classes) were imputed by polytomous regression. We used the incompatible Gibbs sampler³⁰ as implemented in Multivariate Imputation by Chained Equations (MICE).³¹ We used single imputation, which allows for valid point estimates, but not for confidence intervals or statistical tests. A 3rd problem was that neither study had collected direct information about the frequency of visits to the physician. We constructed a logistic regression model using the 34,152 respondents older than 20 years, taken from the Dutch Health Interview Survey 1990–1995 of

the Netherlands Central Bureau of Statistics. The model predicts the probability of visiting the physician during the past year given age, sex, smoking, diabetes, cardiovascular history, being treated for hypertension, and BMI. The value of a random draw from the binomial distribution, with the individual predicted probability as its parameter, was added to the combined data set. A redraw of 11,983 respondents was made from the combined data set such that that age and sex distributions corresponded to the Dutch population of 20 years or older per 1 January 2000. Each person in the microsimulation sample thus corresponded to 1000 real people in the population.

Procedures for screening and subsequent treatment of hypertension, such as those presented in Figure 1 or variations therefore, were implemented in a computer program. For every person in the microsimulation sample, the program calculates if the person enters the screening procedure, how many times the BP is measured, the height of each BP measurement, the diagnosed hypertension status, and whether intervention by drug treatment is indicated.

The model uses the Framingham risk equations¹⁵ to simulate individual patient histories over a period of 10 years. These equations predict the probability of cardiovascular mortality and morbidity as a function of BP, age, sex, smoking, LDL/HDL ratio, diabetes, and left-ventricular hypertrophy. Table 3 provides a description of the 6 endpoints of the Framingham equations. To assess how well the Framingham equations apply to the Dutch population, the predicted 5-year incidence was compared to longitudinal data from the University of Amsterdam (1985–1994, 95,000 person years).³² Except for some minor deviations, it turned out the Framingham equations closely predicted the observed Dutch 5-year incidence, but minor adjustments were needed for the older groups. Table 3 provides age-adjusted calibration factors. The goal of drug treatment is to lower future mortality and disease risks. Per endpoint, a risk reduction factor is estimated based on an extensive meta-analysis on the direct treatment effect on each endpoint.¹⁶ For example, 751 infarcts occurred in treatment groups ($n = 163,453$) and 884 infarcts occurred in control groups ($n = 161,250$), so the risk reduction of treatment is $(751/163,453)/(884/161,250) = 0.838$ (i.e., the number of infarcts reduces by 16.2% as a result of

Table 4 Intermediate Health Outcomes of the Microsimulation Model, Their Definition in Terms of the Framingham Endpoints, Costs Per Year (in Euros) Per Event in the 1st Year and in Later Years, and the Utility Used for Calculating Quality-Adjusted Life Years (QALYs)

Name	Outcome Description	Definition	1st Year	Later Years	Utility
CHDDeath	Coronary heart disease death (e.g., by MI)	CHDD	1507	0	0
CVDDeath	Other cardiovascular disease death (e.g., STROKE)	CVDD-CHDD	3176	0	0
OtherDeath	Death through other causes	MORT-CVDD	908	0	0
MI	Myocardial infarction	MI	12,592	3449	0.79
CHDR	Other coronary heart disease (e.g., angina pectoris, coronary insufficiency)	CHD-MI-CHDD	2269	1134	0.79
STROKE	Stroke, including transient ischemic attack	STROKE	24,058	9115	0.39
CVDR	Other CVD	CVD-CHD-STROKE	2269	1134	0.84

treatment). The last column of Table 3 lists the risk reduction factors used by the simulation model.

After the individual risk on each Framingham endpoint is calculated, the model derives 7 intermediate health outcomes and 3 mortality and 4 morbidity measures. Table 4 defines how each of these is expressed in terms of Framingham endpoints. The term *MORT* in the definition of “OtherDeath” is not from the Framingham study but represents the survival probability (all death causes) per age and sex, calculated from the life tables over the year 1998 for the Netherlands.³³ The other columns of Table 4 list the costs per year of an event in euros in the 1st year and in each subsequent year,¹⁰ as well as the utility values used to calculate the QALY per person.²¹

The individual mortality and disease probabilities are aggregated to the population and subgroup levels. The model calculates the absolute incidence as 1000 times the sum of probabilities over all persons in the sample. The NNT is the number of patients who should be treated to prevent 1 cardiovascular event and is calculated as the inverse of the risk difference in the treated group. The NNS is the number of people who must be screened (and treated if indicated) to

prevent 1 cardiovascular event²⁰ and is calculated as the inverse of the risk difference in the entire population. Risk difference is expressed relative to the null model (scenario “freeze”). The life expectancy of each survivor is calculated from his or her age and sex using life tables.³³ To account for increased mortality in the diseased, the mortality quotient is multiplied by the risk of dying when having the disease relative to the risk of dying when healthy. The following relative risks were estimated from the MORGEN study and used in the calculation of life expectancy: MI (male 2.5, female 4.0), CHDR (male 2.4, female 3.8), STROKE (2.0), and CVDR (2.0). Quality-adjusted life expectancy was calculated in the same way, with the difference that partial instead of full years are counted when morbidity occurs. The utility values per morbidity state are given in Table 3. Healthy life expectancy was calculated by counting only the healthy, here defined as non-CVD, life years.

A much more extensive report (in Dutch) on the model and its results has been written by the authors³⁴ and is available upon request.

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